PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/009281	18.08.2004	18.08.2003

International Patent Classification (IPC) or both national classification and IPC
C12N5/08, A61K39/00, A61P35/00

Applicant
GLYCOTOPE GMBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ The International Searching Authority has not been able to consider the validity of the priority claim because a copy of the earlier application whose priority has been claimed was not available to the International Searching Authority at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

   see separate sheet

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 18-20,22

because:

☒ the said international application, or the said claims Nos. 18-20,22 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3
	No:	Claims	1,4-8,11-22
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	18,19,20,22

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item II

Priority

The international application PCT/EP2003/009140 published as WO2004/018659 has been filed on the 18.08.03 which is the exact date of the priority of the present application. In the two applications the effective filing date as far as the cell lines NM-F9 and NM-D4 are concerned is the same day, the 18.08.03 since in the application PCT/EP2003/009140 there is no reference to these cell lines in the priority document.

The application PCT/EP2003/009140 has now entered the regional phase with the application number EP03792365.3. When entering regional and national phase with the present application the applicant will have to chose to further proceed with only one of the two applications in order to avoid the juridical uncertainty of double patenting.

Re Item III

Non-establishment of opinion with regard to industrial applicability

Claims 18, 19, 20 & 22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: ICHIYAMA M: "Induction of non-HLA-restricted anti-tumor effector cells with strong cytotoxic activity using MUC1/B7 cotransfected K562 cells" KAREI IGAKU KENKYUSHO ZASSHI, JP, vol. 51, no. 3-4, 2000, pages 93-110, XP001182213

D2: WO 97/40182 A (PECHER, GABRIELE) 30 October 1997

D3: KARSTEN et al: "Enhanced binding of antibodies to the DTR motif of MUC1 tandem repeat peptide is mediated by site-specific glycosylation", 1998, XP002112486

D4: BOEHM et al: "Carbohydrate recognition on MUC1-expressing targets enhances cytotoxicity of a T cell subpopulation", 1997, XP002323076

D5: DUK MARIA ET AL: "Purification of human anti-TF (Thomsen-Friedenreich) and anti-Tn antibodies by affinity chromatography on glycophorin A derivatives and characterization of the antibodies by microtiter plate ELISA", 1998, XP008045186

NOVELTY

Document D1 discloses the cell line K562 cotransfected with human MUC1 and with human B7 (Figure 1) and its use as a cancer vaccine (Figures 1-11). Even if the expression of TF and glycophorin has not been tested, it is possible that these antigens are expressed by the K562 cell line disclosed in D1. Further characterizing a product does not render it novel. Therefore claims 1-5 are not novel over D1. Coculturing PBMCs from healthy donors with irradiated MUC1/B7 cotransfected K562 cells is disclosed in D1. Part of the PBMCs are dendritic cells, which anticipates the novelty of claim 10. As a consequence the subject-matter of claims 1,2, 4-8 and 10-19 is not considered to be novel over D1.

Document D2 discloses a vaccine consisting of human, autologous dendritic cells transfected with a partial sequence of the human mucine-MUC1 gene which contains several tandem repeat nucleotide sequences of MUC1 (p.4, l.26 - p.5, l.9). Claims 1,2, 4-9, 11-13 and 15-22 are therefore not novel over D2.

Document D3 discloses antibodies recognizing the glycosylated DTR motif in MUC1. Several glycopeptides which were synthesized for reexamining the antigenicity of the immunodominant region of MUC1 are anticipating the subject-matter of claims 8 and 11-13, 15, 19-22.

Since the cell lines NM-F9 and NM-D4 were obtained after mutagenesis (p.44 of the description) it is highly likely that they are different than the cotransfected MUC1/B7 K562 cells disclosed in D1. Therefore claim 3 is considered to be novel.

INVENTIVE STEP

The subject-matter of claim 3 differs from the disclosure of D1 by the fact it relates to the deposited cell lines NM-F9, NM-D4 or subclones (alternatives a b & c). NM-F9 were shown to express TF while K562 were not (Figure 1 & p.41, l.4 - l.10). Moreover glycophorin A carries the TF-antigen in NM-F9 cells (Figure 4 & p.41, l.29 - p.42, l.5). The effect of the difference

is that the NM-F9 cells are potent cancer vaccine cells stably expressing AGPA (p.6, l.16 - l.22). Whether the K562 cells of D1 express AGPA or not is not known. The problem to be solved by the alternative a of claim 3 is therefore the provision of a modified or mutated K562 cell line. The solution of alternative a (NM-F9) is solving the problem posed and is considered as involving an inventive step for the following reason. Even it the influence of glycosylation on the immunogenicity of TF in MUC1 and in AGPA is known from the prior art (D2 to D5) there is no incentive to apply this teaching while selecting K562 mutants.

As far as characterization of NM-D4 is concerned mainly experimentation carried out with PankoMab has been reported (p.51 - p.53, l.2). Since this monoclonal antibody was not accessible to the public, no comparable difference can be associated with NM-D4. The alternative b of claim 3 though solving the problem of providing a modified or mutated K562 cell line is considered to be an arbitrary selection, thereby not involving an inventive step. Since the description does not disclose subclones of NM-F9 or of NM-D4, the alternative c of claim 3 is not supported by the description and is not solving the technical problem, thereby not involving an inventive step.

INDUSTRIAL APPLICABILITY

For the assessment of the present claims 19-22 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

TA-MUC1 is an internal designation. It is defined on page 4 of the description by referring to PCT/EP03/08014. However this application has been published on the 29.01.04, after the priority date. TA-MUC1 is also defined on page 9 by being detectable by PankoMab,

described in an article (Christensen A et al, Protein Expr Purif, In press) unpublished at the filing date and still unpublished when the search report has been issued. This antibody is therefore not considered as being accessible to the skilled person. There is therefore no enabling disclosure for the TA-MUC1 antigen. The part of the application related to the TA-MUC1 could therefore not be reproduced by a skilled person at the priority date, which does not fulfil the requirements of Article 5 PCT.

Cells have been obtained while using the antibody PankoMab (page 44, l.22 & l.31) which was not available to the public at the filing date. The description does therefore not allow any reproducibility and the cell lines NM-F9 and NM-D4 are considered reproducible only via access to their deposit number. As a consequence only a claim limited to the deposited cell lines may fulfil the requirements of Article 5 PCT. No generalisation is acceptable on the basis of this lack of reproducibility. Among claims 1-5 only alternatives (a) and (b) of the present claim 3 are therefore considered as fulfilling the requirements of Article 5 PCT.

In regional phase the applicant will have to submit a document attesting that the depositor, Nemod Biotherapeutics (p.8, l.26), has authorised the applicant to refer to the deposited biological material in the application and has given his unreserved and irrevocable consent to the deposited material being made available (Rule 28(1) (d) EPC) to the public in order to fulfill the requirements of Rule 28 EPC.

Re Item VIII

Certain observations in the international application (clarity)

It appears clear from D4 (abstract & p.32, right-hand column) and D5 (abstract) that TF is an antigen that is detected on underglycosylated MUC1 and on glycophorin A after desialylation. The wording used in claim 1 does not suggest that TF is part of MUC1 and of glycophorin, which leads to a lack of clarity.

The term "TA-MUC1" is considered to be an internal designation that has no clear meaning for the skilled person. Claim 2 is therefore not considered to fulfil the requirements of article 6 PCT. See also the remark under point VII.

Claim 8 is vague and unclear and has no support in the description, thereby contravening article 6 PCT.